

U.S. Appln. S.N. 10/534,988
AMENDMENT

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REMARKS

This Amendment cancels claims 11-15, 18 and 23-27, amends claims 16, 17 and 19, and adds new claim 28. The "local inflammatory reaction" feature of claim 16 is supported by page 8, lines 3-14. "Systemic inflammatory disease" has been deleted from claim 17, while the amendment of claim 19 merely changes the dependency of that claim. The cis-urocanic acid feature of new claim 28 is supported by page 6, line 6. Claims 16, 17 and 19-22 are pending.

Non-elected claims 11-15 and 23-27 have been canceled, subject to the applicants' right to file a divisional application directed to their subject matter.

The 35 U.S.C. § 103 rejection of claims 17-22 over U.S. Patent No. 5,494,676 to Stab et al. in view of "Mastitus", Stedman's Medical Dictionary (2002) is respectfully traversed. The inventors have unexpectedly discovered that urocanic acid (UCA) accumulates in unbound and non-metabolized form in the cytosol, that cis-UCA acidifies intracellular pH at extracellular pH 6.5, and that an acidic intracellular pH suppresses the immune response. Accordingly, the claimed method includes the administration of a pharmaceutical composition comprising a pharmaceutically acceptable

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agent or salt thereof capable of acidifying cell cytoplasm, wherein an effective amount of the agent is administered in an essentially non-dissociated form to a person or animal, and wherein the agent is mixed with a carrier to adjust the pH of the composition to a pH range of 6.1 to 7.0.

The cited combination of references fails to raise a prima facie case of obviousness against the claimed method because neither reference discloses or suggests the 6.1 to 7.0 pH range feature of the pharmaceutical composition used in the claimed method. Col. 7, lines 24-29 of Stab et al. mention cis-urocanic acid was made from trans-urocanic acid by isomerization in distilled water buffered with NaOH to pH 6.9. However, this is the pH of the reaction medium during cis-urocanic acid synthesis; it is not the pH of a pharmaceutical preparation containing cis-urocanic acid and other ingredients. Stab et al. contains 17 examples of pharmaceutical preparations comprising cis-urocanic acid in combination with different carriers. Yet none of them disclose the pH of their preparations, and there is no recognition that acidifying the cytosol's pH will suppress immune response.

Col. 2, line 62 to Col. 3, line 4 of Stab et al. disclose it is advantageous to add unsaturated fatty acids to its composition.

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However, the basic chemistry of fatty acids teaches that long chain fatty acids, including stearic acid, oleic acid, gamma-linolenic acid, eicosapentaenoic acid and docosahexaenoic acid are practically insoluble in water (see, for example http://en.wikipedia.org/wiki/Fatty_acids). Therefore, it is commonly known that the long chain fatty acids have very little effect on the pH of an aqueous solution. In contrast, cis-urocanic acid is a highly hydrophilic and water-soluble molecule. In general, in an oil/water-emulsion, a hydrophilic compound is found in the water phase of the emulsion and a hydrophobic (i.e. lipophilic) compound is in the oil (lipid) phase of the emulsion. In an O/W--emulsion disclosed in the Example 17 by Stab et al., practically all cis-urocanic acid is located in the water phase of the O/W-emulsion. On the other hand, the long chain fatty acid, such as stearic acid, is located in the oil phase of the O/W-emulsion, where it has no effect on the pH of the water phase. Therefore, it is not possible that the long chain fatty acids were included in the pharmaceutical compositions of Stab et al. to adjust the pH of the water phase and to ensure that cis-urocanic acid is in an essentially undissociated form when administered to a person.

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There is a vast amount of data available on the advantageous health effects of long chain unsaturated fatty acids, such as omega-3-fatty acids (e.g. eicosapentaenoic acid and docosahexaenoic acid) and omega-6-fatty acids (e.g. gamma-linolenic acid). Especially, it is known that these fatty acids have an anti-inflammatory effect in the skin, which is based on the fact these fatty acids are able to react with enzymes that normally metabolize arachidonic acid to produce substances that increase inflammation and itching. In other words, in the presence of the long chain fatty acids, less inflammatory substances are produced. Therefore, it is not surprising the addition of unsaturated fatty acids increased the anti-inflammatory effect in the Examples disclosed by Stab et al.

In short, the long chain fatty acids in the pharmaceutical compositions of Stab et al. were not added to control the dissociation status of cis-urocanic acid, but to produce an anti-inflammatory effect by a direct action of fatty acids on inflammation.

The deficiencies of Stab et al. are not remedied by Mastitis, which merely defines the term. One of ordinary skill in the art is given no suggestion that the pH of a pharmaceutical composition

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containing cis-UCA should be adjusted to 6.1 - 7.0 to maintain cis-UCA in its undissociated form so as to permit it to acidify cell cytoplasm, or that the immune reaction will be suppressed by acidifying the cell's cytoplasm. Reconsideration and withdrawal of the obviousness rejection of claims 16-22 are earnestly requested.

The provisional obvious-type double patenting rejection of claims 16-22 over claims 13-18 and 20-23 of copending Application S.N. 11/408,056 in view of Granstein, "Psoriasis: Further Evidence of a Key Role for Leukocytes," 98 J. Clin. Invest. 1695-1696 (1996) is respectfully traversed. As noted in the Official Action, the allegedly conflicting claims have not yet been allowed. Since this application is in condition for allowance, the rejection should be withdrawn. A corresponding non-provisional rejection can then be made in the '056 application, if appropriate. Reconsideration and withdrawal of the provisional, obvious-type double patenting rejection of claims 16-22 over claims 13-18 and 20-23 of the '056 application in view of Granstein are earnestly requested.

The provisional obvious-type double patenting rejection of claims 16-22 over claims 16-21 and 23-26 of copending Application S.N. 10/565,202 in view of Granstein is respectfully traversed. As noted in the Official Action, the allegedly conflicting claims have

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not yet been allowed. Since this application is in condition for allowance, the rejection should be withdrawn. A corresponding non-provisional rejection can then be made in the '202 application, if appropriate. Reconsideration and withdrawal of the provisional, obvious-type double patenting rejection of claims 16-22 over claims 16-21 and 23-26 of the '202 application in view of Granstein are earnestly requested.

This Amendment overcomes the 35 U.S.C. § 112, first paragraph, rejection of claims 16-22. More particularly, claim 16 has been amended to specify the treatment or prevention of a disease or disorder characterized by local inflammatory reaction; Page 8, lines 4-14 list illustrative diseases or disorders.

Stab et al. is evidence that one of ordinary skill in the art would not be required to perform undue experimentation in order to prevent a disease or disorder characterized by local inflammatory reaction curable by immunosuppression. See, for example, Col. 8, lines 16-22. Prophylactic application of a composition according to the claimed method should not entail any more experimentation than that required for treatment of inflammation. Thus, for example, one of ordinary skill in the art would not be required to perform undue experimentation to prevent an allergic reaction by

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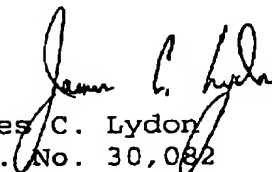
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acidifying the cell's cytoplasm prior to suffering an bee sting, as compared to treating inflammation caused by the bee sting. Reconsideration and withdrawal of the non-enablement rejection of claims 16-22 are earnestly requested.

It is believed this application is in condition for allowance. Reconsideration and withdrawal of all rejections of claims 16-22, and issuance of a Notice of Allowance directed to claims 16, 17 and 19-22, are earnestly requested. The Examiner is urged to telephone the undersigned should he believe any further action is required allowance.

It is not believed any fee is required for entry and consideration of this Amendment. Nevertheless, the Commissioner is authorized to charge our Deposit Account No. 50-1258 in the amount of any such required fee.

Respectfully submitted,


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